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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Mike A. Clark

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WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE, 46TH FLOOR
1650 MARKET STREET
PHILADELPHIA, PA 19103

EXAMINER

DAVIS, MINH TAM B

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/775,693	Applicant(s) CLARK ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,6,7,27 and 31-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,6,7,27 and 31-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened, because the Office action of 06/15/05 was inadvertently cited as a final rejection. The Office action of 06/15/05 should have been a non-final rejection, because the reference by Oyanagi et al was removed to simplify the rejection.

It is noted that applicant has paid for a Notice of Appeal. Applicant can either request a refund or place the funds on credit for future appeals.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1-2, 6-7, 27, 31-36 are examined in the instant application.

Claim Rejections - 35 USC § 103, New Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1-2, 6, 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01, of record, in view of Filpula et al (US 5,804,183, filed on 01/31/97), of record, and further in view of O'brien, WE, 1979 (Biochemistry, 18(24): 5353-6).

Claim 1 is drawn to a method for identifying a cancer patient susceptible to arginine deprivation therapy, comprising detecting, in a cancerous tumor sample of a cancer patient, the presence or absence of argininosuccinate synthetase protein, wherein the absence of argininosuccinate synthetase protein in said sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy, and the presence of argininosuccinate synthetase protein in said sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

Claim 2 is drawn to the method of claim 1, wherein said method further comprises detecting the presence of argininosuccinate synthetase protein in a non-cancerous sample of the corresponding tissue from the cancer patient, wherein the absence of argininosuccinate synthetase protein in said non-cancerous and cancerous tumor samples is indicative of a cancer

patient who is a candidate for arginine deprivation therapy, wherein the presence of argininosuccinate synthetase protein in said non-cancerous sample and the absence of argininosuccinate synthetase protein in said cancerous sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy, and wherein the presence of argininosuccinate synthetase protein in said cancerous sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

Claim 6 is drawn to the method of claim 1, using Western blot, ELISA, enzyme assays, slot blotting, electrophoresis, or immunochemistry.

Claim 27 is drawn to the method of claim 1, wherein the detection of argininosuccinate synthetase protein is by an antibody specific for said protein, or portion thereof.

Sugimura et al teach that arginine deiminase (AD) is a potent inhibitor for some but not all tumor cell lines in vitro (abstract). Further, one would have concluded that **high sensitivity to AD treatment correlates with the absence or low level of the enzyme argininosuccinate synthetase (ASS)** gene expression from the following teaching of Sugimura et al (Sugimura et al, abstract, p.194, second column, first paragraph under "Discussion"). Sugimura et al teach that among the five melanoma cell lines tested that are sensitive to AD treatment, the enzyme argininosuccinate synthetase (ASS) gene expression, as detected by PCR, is also reduced, being almost absent in four cell lines, and at low level in one cell line G361 (abstract, p.192, first column, second paragraph). It is noted that the melanoma cell line G361, having a relatively higher level of ASS expression than the other four melanoma cell lines (1/5 fold lower ASS than that of the control TL-Mor, Sugimura et al, p. 194, second column, first paragraph), although is still sensitive to AD, however, the level of its sensitivity to AD treatment is much less than that

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of the other four melanoma cells, that do not have ASS or have lower level of ASS (A375 has 1/34 fold lower than that of the control TL-Mor, Sugimura et al, p. 194, first column, last paragraph). That is, the melanoma cell line G361 requires a much higher level of concentration of AD, shows “a marginal response” , i.e. a reduction to 23% of control cell proliferation at 130 ng/ml of AD, as compared to a level of 16 ng/ml, or 32 ng/ml of AD, which AD level almost completely inhibits cell proliferation of the other four melanoma cell lines (Sugimura et al, p.193, first column, paragraph before last). It is further noted that the Hela epithelial carcinoma cell line, having even a higher level of ASS than the marginal melanoma cell line G361 (1/3 fold lower versus 1/5 lower than that of the control TL-Mor) is not sensitive to AD treatment (figure 4 and p.194, second column, first paragraph), thus confirming a correlation between the level of ASS and sensitivity to AD treatment. In other word, the higher the level of ASS, the less sensitivity to AD treatment, and that at the ASS level of Hela cells, at 1/3 fold less than that of the control cells, one do not see sensitivity to AD treatment. This correlation between sensitivity of AD treatment and low level of ASS gene expression is found not only in the melanoma cell lines, but is found as well in blood peripheral lymphocytes that are sensitive to AD, as confirmed by the teaching of Sugimura et al that the blood peripheral lymphocytes that are sensitive to AD, “because” they have extremely low level of ASS (Sugimura et al, p.191, second column, last four lines bridging p.192). In addition, Sugimura et al teach that melanoma cell lines have high sensitivity to AD treatment, because of their inability to utilize C-citrulline, which is converted to arginine by the enzyme ASS, which arginine is essential for survival of many mammalian cells (p.191, second column, bridging p.192).

Sugimura et al do not teach a method for identifying a cancer patient susceptible to arginine deprivation therapy, comprising detecting ASS protein, wherein the absence of ASS in the cancerous tumor sample is indicative that the patient is a candidate for arginine deprivation therapy.

US 5,804,183 teaches treating of carcinoma that are deficient in ASS, and melanoma, using AD (claims 7-10). US 5,804,183 teaches a method for reducing the level of arginine comprising administering arginine deaminase (AD) (claim 5). In other words, treating with AD, which reduces the level of arginine, is the same as arginine deprivation therapy.

O'brien teaches detection of argininosuccinate synthetase in human liver, using an antibody specific for argininosuccinate synthetase, by electrophoresis analysis.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to screen for cancers that are deficient in argininosuccinate synthetase (ASS), to expand the types of cancers that are susceptible to AD and thus treatable by AD, because carcinoma or melanoma, that have low level of argininosuccinate synthetase (ASS), have been successfully treated by AD, which depletes arginine, as taught by US 5,804,183, because not any cancer is susceptible to AD treatment, as taught by Sugimura et al, and because the absence or low level of ASS is correlated with susceptibility to AD treatment, in view of the teaching of Sugimura et al, and further because the enzyme ASS is crucial for the biosynthesis of arginine, the presence of which is essential for cell survival, as taught by Sugimura et al, and thus one would have expected that the absence or low level of ASS, resulting in low level of synthesized arginine in cells, would make the cells susceptible to further arginine depletion by AD treatment.

Further, it would have been obvious to detect the ASS protein, using the antibody specific for said protein, as taught by O'Brien et al, in addition to detect the mRNA level, as taught by Sugimura et al, to expand the versatility of the method to identify cancer patients that are susceptible to AD treatment.

One would have a reasonable expectation of success, because although Sugimura et al only teach that the level of ASS gene expression is detected by PCR (p.192, second column, last paragraph), the absence of the ASS mRNA taught by Sugimura et al would correlate with the absence of ASS protein.

2. Claims 6-7, 31-32, 35, 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01, in view of Filpula et al (US 5,804,183, filed on 01/31/97), and O'Brien, WE, 1979 (Biochemistry, 18(24): 5353-6) and further in view of Thompson et al (US 5,424,192, filed on 03/29/93).

Claim 6-7 are drawn to the method of claim 1, using Western blot, ELISA, enzyme assays, slot blotting, electrophoresis, or immunochemistry.

Claims 31-32, 35-36 are drawn to the method of claim 27, wherein the antibody has a detectable label (claim 31), which is radioactive, fluorescent or chromomorphous (claim 32), or an enzyme (claim 35) or has a visible color (claim 36).

The teaching of Sugimura et al, US 5,804,183, and O'Brien has been set forth above.

Sugimura et al, US 5,804,183 and O'Brien do not teach that argininosuccinate synthetase protein is detected by an antibody specific for said protein, using Western blot, ELISA, enzyme assays, slot blotting, or immunochemistry. Sugimura et al, US 5,804,183 and O'Brien do not

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teach that the antibody has a detectable label, which is radioactive, fluorescent or chromomorphpic, or an enzyme, or has a visible color.

US 5,424,192 teaches a method for detecting prostate cancer, which is an EIA, ELISA, a Western blot, a slot blot, or an IRA (see claim 12), using an antibody that is labeled with a detectable label, such as a radioisotope, a fluorescent chemical, an enzyme, a chromatic chemical (see claim 29).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to use Western blot, ELISA, enzyme immunoassays, or slot blotting, as taught by US 5,424,192, besides electrophoresis taught by O'brien for detecting argininosuccinate synthetase protein, wherein the antibody taught by O'brien is labeled with a radioisotope, a fluorescent chemical, an enzyme, or a chromatic chemical, using the method taught by US 5,424,192, to increase the versatility of the method to identify cancer patients that are susceptible to AD treatment.

3. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01, in view of Filpula et al (US 5,804,183, filed on 01/31/97), and O'brien, WE, 1979 (Biochemistry, 18(24): 5353-6) and further in view of Diamandis et al (US 6,068,830, having its PCT filed on 07/14/1994).

Claim 33 is drawn to the method of claim 31, wherein said detectable label is I^{131} , I^{125} , C^{14} , S^{35} , P^{32} , or P^{33} .

The teaching of Sugimura et al, US 5,804,183, and O'brien has been set forth above.

Sugimura et al, US 5,804,183 and O'brien do not teach that argininosuccinate synthetase protein is detected by an antibody, which is labeled with I^{131} , I^{125} , C^{14} , S^{35} , P^{32} , or P^{33} .

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Diamandis et al teach a method for imaging cancer, using an antibody that is labeled with a radioisotope, wherein said radioisotope includes I^{131} , I^{125} , C^{14} , S^{35} , P^{32} , or P^{33} (claim 4).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect argininosuccinate synthetase protein, using the antibody taught by O'Brien, wherein the antibody is labeled with a radioisotope, such as I^{131} , I^{125} , C^{14} , S^{35} , P^{32} , or P^{33} , as taught by Diamandis et al, to increase the versatility of the method to identify cancer patients that are susceptible to AD treatment.

4. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01, in view of Filpula et al (US 5,804,183, filed on 01/31/97), and O'Brien, WE, 1979 (Biochemistry, 18(24): 5353-6) and further in view of Wallace et al (US 6,124,106, filed on 03/10/99) and Hansen et al, 1989 (Electrophoresis, 10 (8-9): 645-52).

Claim 34 is drawn to the method of claim 31, wherein said detectable label is fluorescein, phycolipoprotein, or tetraethylrhodamine isothiocyanate.

The teaching of Sugimura et al, US 5,804,183, and O'Brien has been set forth above.

Sugimura et al, US 5,804,183 and O'Brien do not teach that argininosuccinate synthetase protein is detected by an antibody that is labeled with fluorescein, phycolipoprotein, or tetraethyl rhodamine.

US 6,124,106 teaches a method for detecting cancer, using an antibody that is labeled with fluorescein, phycolipoprotein, or tetraethyl rhodamine (see claim 10).

Hansen et al teach detection of human lymphocytes, using tetraethylrhodamine isothiocyanate-labeled anti-IgG (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detect argininosuccinate synthetase protein, using the antibody taught by O'Brien, wherein the antibody is labeled with fluorescein, or phycolipoprotein, as taught by US 6,124,106, or labeled with tetra-rhodamine isothiocyanate, as taught by Hansen et al to increase the versatility of the method to identify cancer patients that are susceptible to AD treatment.

Answers to Applicant's Arguments

Claim Rejections - 35 USC § 103

A. Applicant argues that the claimed method is not obvious, because it had not been recognized in the art that the level of argininosuccinate synthetase protein expressed in tumor cells could be used to predict whether particular tumors would be sensitive to arginine deprivation therapy. Applicant argues that the art did not teach or suggest that the level of argininosuccinate synthetase protein could be used to determine whether the patient was a candidate for arginine deprivation therapy.

Applicant's arguments in paper of 05/30/06 are not found to be persuasive for the following reasons:

The teaching in the art indicates that level of argininosuccinate synthetase protein expressed in tumor cells could be used to identify whether particular tumors would be sensitive to arginine deprivation therapy, because the absence or low level of ASS is correlated with susceptibility to AD treatment, in view of the teaching of Sugimura et al.

B. Applicant argues that in the teaching of Sugimura et al, the ASS mRNA in G361 melanoma cells was only 20% of the control cell line, but the G361 melanoma cells still

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exhibited “high sensitivity to AD” (page 193, first column, first full paragraph). Applicant argues that in contrast, the level of ASS in the carcinoma cells was 33% of that of the control cells, i.e. but the carcinoma cells were not sensitive to arginine deiminase. Applicant argues that since the ASS level in G361 melanoma cells is only slightly less than that of the carcinoma cells, one would have expected that the carcinoma cells to exhibit sensitivity to arginine deiminase (AD).

Applicant’s arguments in paper of 05/30/06 are not found to be persuasive for the following reasons:

Although the particular Hela carcinoma cells having reduced level of ASS, said level is still higher than that of the melanoma cells G361, that however only have a “marginal response” to AD, even at much higher level of concentration of AD, as compared to other melanoma cells that have much lower level of ASS, or do not show the presence of ASS, *supra*. In other word, the higher the level of ASS, the less sensitivity to AD treatment, and that at the ASS level of Hela cells, at 1/3 fold less than that of the control cells, one do not see sensitivity to AD treatment.

C. Applicant argues that the remaining references do not compensate the deficiencies of Sugimura. Applicant argues that Takaku does not teach the level of ASS in hepatoma and fibrosarcoma however, nor does the reference teach or suggest that the level of ASS could be assessed to determine which tumor types would be sensitive to the growth inhibitory of arginine deiminase (AD).

It is noted that the Takaku reference has been omitted to simplify the issue. Therefore, Applicant’s arguments are moot.

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D. Applicant argues that Filpula et al (US 5,804,183) teaches that AD can be used to treat conditions that are known to respond to arginine deprivation, which include melanoma deficient in ASS. Applicant argues that Filpula does not independently report the level of ASS in carcinoma and melanoma, but cites Sugimura for the proposition that melanoma cells are deficient in ASS. Applicant argues that the patent does not teach or suggest that the level of ASS could be assessed or should be determined to determine which tumor types would be sensitive to the growth inhibitory of arginine deiminase (AD).

Applicant's arguments in paper of 05/30/06 are not found to be persuasive for the following reasons:

Applicant argues individual reference. Filpula et al clearly teach a method for treating carcinoma and melanoma that are deficient in ASS, using AD (claim 9). Thus one would have been motivated to screen for other cancers that are deficient in ASS, because cancers such as carcinoma and melanoma that are deficient in ASS have been successfully treated with AD, as taught by Filpula et al, and because the absence or low level of ASS is correlated with susceptibility to AD, in view of the teaching of Sugimura et al, and further, because not any tumors are susceptible to AD treatment, as taught by Sugimura et al. The motivation is to enhance the efficiency of cancer treatment by AD, because not any tumors are susceptible to AD treatment, as taught by Sugimura et al, and to expand the types of cancers that are susceptible to AD and thus treatable by AD.

E. Applicant argues that Oyangi does not teach that hepatomas are deficient in ASS.

Applicant argues that Oyangi does not teach treating hepatomas with AD, nor teach or suggest

that the level of ASS could be assessed or should be determined to determine which tumor types would be sensitive to the growth inhibitory of arginine deiminase (AD).

It is noted that the Oyangi reference has been omitted to simplify the issue. Therefore, Applicant's arguments are moot.

F. Applicant argues that the Examiner incorrectly asserts that that "high susceptibility to cell killing by AD is correlated with low level as taught by Sugimura". Applicant argues that because HeLa carcinoma cells are not sensitive to AD treatment, and yet have only 33% of ASS as compared to that of the control cells, Sugimura teaches that the level of ASS correlates with high sensitivity to AD in melanoma cells only, and reports that the correlation does not exist in carcinoma cells. Applicant argues that one would not have concluded that the ASS level are necessarily correlated with sensitivity of AD in tumor types other than melanoma.

Applicant argues that the Filpula patent apparently incorrectly interprets the teaching of Sugimura, because Filpula patent states that AD can be used to treat conditions, including carcinoma deficient in ASS, e.g. melanoma, citing Sugimura.

Applicant's arguments in paper of 05/30/06 are not found to be persuasive for the following reasons:

The Examiner apologizes for any confusion made, when reciting that "high susceptibility to cell killing by AD is correlated with low level as taught by Sugimura". Rather, the Examiner meant to state that one would have concluded that "high susceptibility to cell killing by AD is correlated with low level of ASS, in view of the teaching Sugimura".

Contrary to Applicant's arguments, the teaching of Sugimura et al clearly points to a correlation between absence of ASS and susceptibility to AD treatment. Sugimura shows that the

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level of ASS in Hela cells although 1/3 lower than that of the control, is still higher than the 1/5 level of one melanoma cell line G361, which only shows a marginal response (23% of control cell proliferation, instead of almost completely inhibited) even at a much higher concentration of AD (130 ng/ml of AD versus 16 ng/ml or 32 ng/ml of AD), as compared to other four melanoma cells that have even lower level of ASS, i.e. 1/34 fold lower than that of the control cells, or almost absent (Sugimura et al, p.193, first column, paragraph before last). In other words, the lower the level of ASS, the more the sensitivity to AD treatment, thus indicating a correlation between the level of ASS and sensitivity to AD treatment. It is further noted that the Hela epithelial carcinoma cell line, having even a higher level of ASS than the marginal melanoma cell line G361 (1/3 fold lower versus 1/5 lower than that of the control TL-Mor) is not sensitive to AD treatment (figure 4 and p.194, second column, first paragraph), thus confirming a correlation between the level of ASS and sensitivity to AD treatment, i.e. the higher the ASS concentration, the less sensitivity to AD treatment. This correlation between sensitivity of AD treatment and low level of ASS gene expression is found not only in the melanoma cell lines, but is found as well in peripheral blood lymphocytes, as confirmed by the teaching of Sugimura that the lymphocytes are highly sensitive to AD, "because of their extremely low level of expression of the ASS gene " (Sugimura et al, p.191, second column, last four lines bridging p.192).

Further, whether Filpula patent incorrectly interprets the teaching of Sugimura or not is not germane here. Filpula et al clearly teach a method for treating carcinoma and melanoma that are deficient in ASS, using AD (claim 9). Moreover, the teaching of Filpula does not contradict the teaching of Sugimura, because Applicant has not shown that the particular carcinoma

population taught by Sugimura is the same as the carcinoma population that are deficient in ASS taught by Filpula.

G. Applicant further argues that the Examiner is incorrect when asserting that “the AD sensitivity of “various” tumor cells is attributed to the reduced level of ASS, as taught by Sugimura et al”. Applicant argues that Sugimura only teach that melanoma cells that were deficient in argininosuccinate synthetase RNA exhibit sensitivity to AD. Applicant argues that carcinoma cells having reduced level of ASS mRNA were not sensitive to AD. Applicant argues that thus Sugimura do not teach that various tumor cells were sensitive to AD. Applicant argues that one would not have attributed AD sensitivity to low level of ASS, due to the fact that carcinoma cells exhibit low level of ASS relative to the control, but were not sensitive to AD.

Applicant’s arguments in paper of 05/30/06 are not found to be persuasive for the following reasons:

Sugimura et al teach that AD is a potent growth inhibitor for “some” but not all tumor cell lines in vitro, and that as AD catalyses the direct conversion of arginine to citrulline, the AD-sensitivity of “various tumor cells” might be attributed to the levels of urea cycle enzymes involved in arginine biosynthesis (abstract, first six lines, and figure 1 on page 191). Sugimura et al went on and showed that, as an example, in tested melanoma cells, that AD sensitivity of melanoma cells is attributed to the reduced level of ASS (p.194, second column, first paragraph under “Discussion”). Further, not only Sugimura et al show an example of melanoma cells, Sugimura et al teach that peripheral blood lymphocytes are also highly sensitive to AD, “because of their extremely low level of expression of the ASS gene” (p.191, second column, last four lines, bridging p.191).

Further, although the Hela carcinoma cells having reduced level of ASS, said level is still higher than that of the melanoma cells G361, that however only have a “marginal response” to AD, even at much higher level of concentration of AD, as compared to other melanoma cells that have much lower level of ASS, or do not show the presence of ASS, *supra*. In other word, the higher the level of ASS, the less sensitivity to AD treatment, and that at the ASS level of Hela cells, at 1/3 fold less than that of the control cells, one do not see sensitivity to AD treatment.

In addition, one would have expected that various identified cancer cells, that have low level of ASS would be susceptible to AD treatment, because of their low level of ASS, in view of the following teaching:

1) Carcinoma and melanoma, that have low level of ASS, have been successfully treated with AD, as taught by Filpula et al (US 5,804,183),

2) Absence or low level of ASS is correlated with high sensitivity to AD treatment in melanoma cells, in view of the teaching of Sugimura,

3) In addition to melanoma cells taught by Sugimura, peripheral blood lymphocytes are also highly sensitive to AD, “because of their extremely low level of expression of the ASS gene, as taught by Sugimura et al, and


3) The enzyme ASS is crucial for the biosynthesis of arginine, the presence of which is essential for cell survival, as taught by Sugimura et al, and thus one would have expected that the absence or low level of ASS, resulting in low level of synthesized arginine in cells, would make the cells susceptible to further arginine depletion by AD treatment.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
July 20, 2006


JEFFREY SIEW
SUPERVISORY PATENT EXAMINER